Pharmacokinetics of prednisolone in man during acute and chronic exposure to high altitude

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Abstract. Introduction: The exposure to high altitude (H) produces several physiologic alterations which may induce changes in the pharmacokinetics of drugs. This hypothesis has been confirmed in previous studies which suggest that drugs which are highly bound to plasma proteins are most likely to exhibit altered pharmacokinetics. Objectives: To further elucidate the influence of H on pharmacokinetics, prednisolone was selected, since it is highly bound to plasma proteins, renally excreted and poorly bound to red blood cells. Subjects, materials and methods: Prednisolone (80 mg) was given orally to three groups of young healthy volunteers. One group was residing at sea level (L): the same volunteers were studied again after 15 hours of exposure to high altitude (3600 m, HA group), and volunteers living at H for at least six months (group HC). Results: There were no statistically significant differences in the pharmacokinetic parameters calculated from plasma data in the three situations studied. When calculated from whole blood data, however, AUC and C_{max} were increased and both volume of distribution and clearance diminished after exposure to H, either acute or chronically. Binding to proteins increased significantly after H exposure from 57% in group L to 75% and 94% in group H and HC, respectively. Binding to erythrocytes also increased with H exposure from 43.7% in group L to 50.6% and 61.6% in group HA and HC, respectively. The prednisolone/prednisone ratio in urine was 11.1 in group L, 7.3 in group HA and 45.6 in group HC. Conclusion: Since prednisone has very little intrinsic glucocorticoid activity and has to be converted to prednisolone for therapeutic effect, the alteration of the prednisolone/prednisone ratio, as a result of high altitude exposure could be clinically relevant. Additional experiments are desirable to further evaluate this observation.

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Introduction

The ascent to high altitude (H) can lead to acute mountain sickness (AMS), which is characterized by fatigue, anorexia, insomnia, nausea and headache. The pathophysiological features of AMS are complex and may include increased capillary permeability, inflammatory mediator release at high altitude, effects of hypoxia on the gene expression of vasoactive mediators, endothelial activation injury and fluid retention [Hackett and Roach 2001, Maloney et al. 2000, Sutton 1992, Swenson et al. 2002]. The cerebral and pulmonary syndrome that can develop in unacclimatized persons upon rapid ascent to H is potentially fatal. Diverse interactions between genetic factors and the environment most likely explain individual susceptibility or relative resistance to these hypoxia-induced illnesses. Exposure to high altitude has for many years been used as an experimental model for studying the pathophysiologic process of hypoxia in an otherwise healthy population [Hackett and Roach 2001, Jürgens et al. 2002]. The exposure to high altitude and the associated physiological problems are increasing in prevalence and are now a public health problem that has economic consequences because of increased travelling to high altitude locations for sport, tourism or work.

Previous pharmacokinetic studies conducted with meperidine [Ritschel et al. 1996a, 1996b], acetazolamide [Ritschel et al. 1998a, 1998b] and lithium [Arancibia et al. 2003b] at high altitude, indicate altered drug disposition due to increased erythrocyte binding and decreased protein binding and support the

need to extend H pharmacokinetic research to other drugs. Based on these previous results and the physiological changes that the body experiences at H, the drugs most likely to be altered in their disposition are those that are highly protein-bound and renally eliminated weak acids.

Prednisolone is used to treat a variety of problems including adrenal insufficiencies, arthritis, asthma, muscular dystrophy and myasthenia gravis [Hardman and Limbird 1996]. It is unionized under physiological pH conditions and is 80 – 95% protein-bound with an extent of absorption of 82%. Prednisolone is highly metabolized to prednisone and its pharmacokinetics is dose-dependent [Tanner et al. 1979]. It is highly renally eliminated with 26% being eliminated as parent compound. For these reasons prednisolone was selected to continue our research on the effect of H on the pharmacokinetics of drugs.

Subjects, materials and methods

Subjects and study design

Three groups of 12 healthy volunteers each participated in the study. The protocol was approved by the Institutional Review Board of the University of Chile, Santiago, Chile, and the Chilean Armed Forces. All of the volunteers were men recruited from the Chilean Army. The inclusion parameters were a minimum of six months of residence at sea level or H (= 3600 m), completion of physical examination, urinalysis and blood chemistry tests. Acclimatization to high altitude usually occurs over a period of a few days to a few months, therefore, six months of residence were considered sufficient for acclimatization. Exclusion parameters included any results outside the established normal range for urine and blood chemistry tests, any previous gastrointestinal, hepatic, cardiovascular, pulmonary or renal disease, previous severe mountain sickness, and use of any drug in the ten days preceding the study. Group L consisted of volunteers living at sea level (military base at Arica, the northernmost city in Chile). Group HA was formed by the same subjects as group L, but after short-term exposure to high altitude. They were transported by bus, one week after the first phase of the study at sea level, to the military base at Putre in the Andes of North Chile, at 3600 m and 160 km east from Arica. They arrived in the afternoon and the study was performed the following morning. The third group HC comprised subjects who had resided for at least six months at the study site at Putre. Mean (± SD) height was 1.70 (0.1) m for groups L and HA and 1.73 (0.07) m for group HC. Body weight was 66.83 (5.67) kg for group L and HA and 73.17 (9.68) for group HC.

For all groups the treatment was the same: after an overnight fast (12 hours) with water allowed ad libitum, a dose of 80 mg of prednisolone as immediate release tablets was given to each volunteer (Prelone, Asta Medical, Brazil) along with 250 ml of water at a controlled room temperature. Participants were given a standard breakfast two hours after dosing. The meals were the standard 1 in the Army and the same in the two locations. Blood samples were collected via intravenous catheter or individual venipuncture at appropriate intervals during 24 hours.

An aliquot of each blood sample was lyzed for analysis of drug in whole blood. Heparinized blood was centrifuged and plasma separated; 0.5 ml of the plasma samples obtained were filtered through an Amicon Centricom.

Urine samples were collected at 1, 2, 4, 8, 12, 24 and 48 h after dosing, aliquots were separated for each individual at each collection interval.

Plasma, blood and urine samples collected at sea level were immediately frozen after separation. At high altitude, samples were frozen and kept frozen during the stay, they were then packed in dry ice for transportation to the laboratory for analysis.

Analytical procedure

A high-performance liquid chromatographic technique for the simultaneous determination of prednisolone and prednisone in plasma, whole blood, urine and bound to plasma proteins, using betamethasone as internal standard was used. The separation was performed by LichroCART 250-4 Lichrospher Si 60 (Merck) column (250 × 4.6 mm

ID, 5 µm particle size) and LichroCART 4-4 Si 60 (5 µm particle size) guard column (Merck). The mobile phase was a mixture of methanol – glacial acetic acid – dichloromethane (1.5 : 8.0 : 90.5 v/v/v). The flow rate was 1.8 ml/min and the room temperature fluctuated between 15 °C and 20 °C. Detector was set at 254 nm. Liquid-liquid extraction (ethylacetate) was used for whole blood samples and solid phase extraction (Lichrolut RP-18 Merck) was used for plasma, urine and bound to plasma proteins.

The values obtained during six-day validation for repeatability and accuracy were the following. The CV ranged from 2.1% – 3.5% for prednisone and 3.5% – 4.6% for prednisolone in plasma. From 1.1% – 5.7% for prednisone and 3.8% – 8.9% for prednisolone in urine; from 4.3% – 14.6% for prednisone and 4.7% – 13.5% for prednisolone in whole blood, and from 4.3% – 6.7% for prednisone and 2.8% – 6.9% for prednisolone in "plasma proteins".

The limit of quantitation (LOQ) determined by repeated analysis was 100 ng/ml for prednisolone for each biological fluid. For prednisolone the precision at the LOQ was determined as CV = 8.3% and for prednisone 5.3%, the mean relative error (RE) was 13.0% for prednisolone and 17.0% for prednisone in plasma. The CV was 6.0% for prednisolone and 4.3% for prednisone, the mean RE was 17.7% for prednisolone and 18.0% for prednisone in urine. For whole blood the CV was 11.7% for prednisolone and 10.8% for prednisone, the mean RE was 19.4% for prednisolone, and 18.2% for prednisone. The CV was 6.3% for prednisolone and 6.0% for prednisone, the mean RE was 16.6% for prednisolone and 15.2% for prednisone in plasma protein.

The accuracy, precision, specificity, linearity (100 – 1500 ng/ml) and repeatability meet the requirements of current recommendations in bioanalytical method validation [FDA 2001]. The samples were stable for at least three months at –20 °C and to three freezing/thawing cycles.

Pharmacokinetic analysis

The concentration-time data for prednisolone were analyzed by compartment model and noncompartmental analysis using the AUC-RPP and RESID computer programs [Ritschel 1975, 1986]. Extent of protein binding (EPB) was determined using the following equation:

$$EPB = \frac{C_p - C_w}{C_p} \times 100$$

where C_p and C_w are the concentration in plasma, and plasma water, respectively. Binding to erythrocytes was calculated according to the following equation [Ritschel 1992]:

$$C_E = \frac{C_b - C_p(1-H)}{C_b} \times 100$$

where C_E is binding to erythrocytes, and C_b and C_p are concentrations in blood and plasma, respectively, and H is the hematocrit.

Statistical analysis

Each of the pharmacokinetic parameters was subjected to one-way analysis of variance. A level of $p < 0.05$ was considered to be statistically significant.

Results

Both blood chemistry tests and urinalysis were within normal range for all volunteers. The hematocrit was 19.0% and 28.9% higher in group HA and HC, respectively, in comparison with group L, the values being statistically significant. Hemoglobin was increased 12.4% and bilirubin 33.3% in group HC compared with group L, the differences were statistically significant. Total proteins and albumin were slightly higher in group HC in comparison with group L, the differences being not statistically significant. Other blood chemistry values were within the normal ranges (Table 1).

Plasma and whole blood

Figures 1 and 2 show the concentration-time profiles for prednisolone in plasma and whole blood, respectively. Data were best fit by a one-compartment open model. Mean pharmacokinetic parameters in blood and plasma are listed in Table 2. There were no statistically significant differences in the

Table 1. Mean blood chemistry values measured in L and HC group of volunteers (SD = standard deviation).

Parameter	L	SD	HC	SD
Bilirubin (mg/dl)	0.8	0.1	1.0	0.3
Transaminases GPT (UI)	19.7	4.6	28.0	7.9
Transaminases GOT (UI)	25.9	4.1	30.1	10.8
Hematocrit (%)	42.6	4.0	54.9	2.4
Hemoglobin (g%)	14.5	1.0	16.3	0.9
Serum creatinine (mg/dl)	1.0	0.1	1.1	0.1
Total proteins (mg/dl)	7.5	0.4	7.7	1.0
Albumin (mg/dl)	5.1	0.2	5.3	0.7

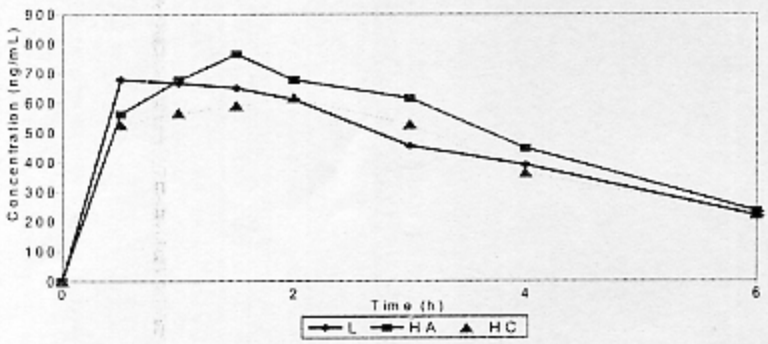

Figure 1. Mean plasma concentration-time profiles for prednisolone in healthy volunteers at low altitude (L), after short-term exposure to high altitude (HA), and after long-term exposure to high altitude (HC).

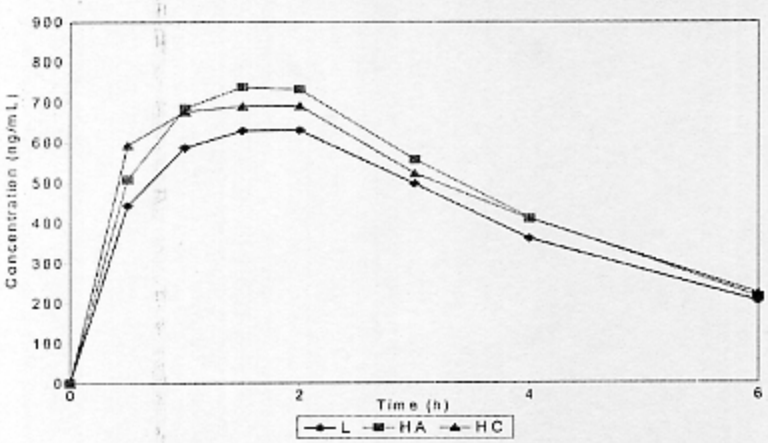

Figure 2. Mean whole blood concentration-time profiles for prednisolone in healthy volunteers at low altitude (L), after short-term exposure to high altitude (HA), and after long-term exposure to high altitude (HC).

pharmacokinetic parameters calculated with plasma data in the three situations studied. The concentration-time profiles in whole blood in groups L, HA and HC have similar shapes. AUC is increased after exposure to high altitude either acute (12.8%) or chronically (13.5%). The differences were statistically significant when HA or HC were compared to group L. C_{max} is also higher in groups HA (16.9%) and HC (14.1%), and the difference in the two groups with respect to group L is statistically significant. Both, volume of distribution and clearance diminish at high altitude, and the differences are statistically significant when one compares the values obtained in groups HA (20.4% and 15.6%, respectively) and HC (25.2% and 15.6%, respectively) with those of group L. Ka tends to be higher after exposure to H, but the differences are not statistically significant.

Binding to erythrocytes

The binding of prednisolone to erythrocytes was 43.7% ± 14.6% in the group at sea level and increased to 50.6% ± 12.1% after short-term exposure to high altitude, and to 61.6% ± 12.6% after chronic exposure. The differences are statistically significant when one compares H vs. L, HC vs. L and H vs. HC.

Binding to proteins

Binding of prednisolone to plasma protein was measured in nine subjects of group L and in all the volunteers in groups HA and HC. The measures were made at 1.0, 1.5 and 2.0 hours after dosing. Binding was 57% ± 1.8% at sea level and increased to 75% ± 6.9% in group HA and to 94% ± 8.8% in group HC. The differences are statistically significant when comparing sea level group vs. the situations after either short- or long-term exposure to H.

Urinary excretion

The sea level group excreted 9.22 ± 3.55 mg of unchanged prednisolone in the urine which increased to 15.84 ± 6.26 mg in group HA and was 7.75 ± 2.72 mg in group HC. The excretion of prednisone was 0.83 ± 0.82 mg for group L, 2.17 ± 2.86 mg for group HA and 0.17 ± 0.12 mg for group HC.

Discussion

The influence of H on the pharmacokinetics of prednisolone has been demon-

Table 2. Mean pharmacokinetic parameters of prednisolone in healthy volunteers in plasma and whole blood at low altitude (L), after short-term exposure to high altitude (HA), and after long-term exposure to high altitude (HC). The values in parenthesis are the SD.

	Plasma			Blood		
	L	HA	HC	L	HA	HC
K_{el} (1/h)	0.28 (0.04)	0.30 (0.10)	0.30 (0.09)	0.32 (0.04)	0.34 (0.04)	0.32 (0.04)
$t_{1/2}$ (h)	2.51 (0.37)	2.55 (0.84)	2.57 (0.87)	2.18 (0.28)	2.09 (0.23)	2.21 (0.36)
Ka (1/h)	1.59 (0.58)	1.78 (1.06)	1.28 (0.66)	1.78 (0.50)	1.95 (0.72)	2.28 (1.34)
$t_{1/2abs}$ (h)	0.50 (0.22)	0.59 (0.55)	0.69 (0.34)	0.42 (0.10)	0.41 (0.16)	0.38 (0.17)
Cl/F (ml/min)	387.63 (55.48)	357.91 (107.71)	439.96 (117.68)	440.84 (82.88)	381.21 (35.08)	381.42 (43.94)
Vd_{area}/F (l/kg)	1.27 (0.31)	1.13 (0.24)	1.27 (0.35)	1.24 (0.27)	1.03 (0.07)	0.99 (0.13)
AUC (μg/ml × h)	3.51 (0.54)	3.99 (0.97)	3.47 (1.23)	3.12 (0.55)	3.52 (0.32)	3.54 (0.45)
MRT (h)	4.19 (0.58)	4.31 (1.07)	4.46 (1.08)	3.81 (0.58)	3.71 (0.45)	3.80 (0.55)
C_{max} (μg/ml)	0.93 (0.64)	0.87 (0.17)	0.78 (0.32)	0.71 (0.11)	0.83 (0.09)	0.81 (0.06)
t_{max} (h)	1.50 (0.8)	1.50 (0.9)	1.80 (1.2)	1.50 (0.5)	1.70 (0.6)	1.50 (0.7)

strated in this study. The pharmacokinetic parameters K_{el}, $t_{1/2}$, C_{max}, MRT found in the volunteers at sea level when measured in plasma are in agreement with those described for a comparable dose of prednisolone administered to healthy subjects [Bergrem 1983, Rose et al. 1981, Tanner et al. 1979]. C_{max} in one volunteer at sea level (subject 5) was three times higher than the mean, however, the maximal concentration found in the same subject after short-term exposure to H was close to the average value of the group. Absorption was rather rapid in the three situations studied with an absorption half-life around 0.5 h except in one subject of group HC who showed a lag time of one hour. We did not find statistically significant differences in the pharmacokinetic parameters obtained from plasma data when comparing sea level group with those subjects after either short- or long-term exposure to altitude.

There is no literature information about the pharmacokinetic parameters of prednisolone obtained from whole blood data. The values obtained in the subjects at sea level are very similar to those calculated from plasma data with the exception of clearance which is higher and probably is the cause for lower AUC, C_{max} and MRT. The exposure to high altitude, either for a short or a long term, causes an increase in the AUC and C_{max} and the differences are statistically significant. On the other hand, both clearance and volume of distribution, diminish significantly in the high altitude.

Several studies have characterized dose-dependent protein binding of prednisolone [Rose et al. 1981, Tanner et al. 1979, Wald et al. 1992]. Prednisolone binds mainly to transcortin and albumin. Nonlinear protein binding occurs because of the saturation of transcortin binding which is produced as prednisolone concentrations rise. At low concentrations, a 95% binding has been reported, at higher concentrations the low affinity albumin component yields a fraction bound near 60% [Wald et al. 1992]. Nonlinear protein binding of prednisolone in the range of concentrations was measured in this study. At sea level, when prednisolone concentrations were between 400 and 500 ng/ml, the binding was 62.7 ± 10.7% and diminished to 45.6 ± 11.9% when concentrations rose to 700 – 800 ng/ml. The values for the same ranges of concentration in group HA were 91.2 ± 18.9 and 60.9 ± 19.8, respectively. We measured the binding at 1.0, 1.5 and 2.0 hours after the administration of prednisolone. We calculated the mean for each of the three sample times and then the data were collected in order to obtain a general mean. Our results in the volunteers at sea level were 57 ± 1.81%, HA 75.0 ± 6.85% and HC 93.9 ± 8.75%. We found differences statistically significant between L and HC. The mean values of both total proteins and albumin determined in the group exposed chronically to the altitude were not statistically significantly different from those in the group at sea level. On the other hand, bilirubin, which also binds to albumin and could reduce protein binding of prednisolone, is increased in group HC. Other studies have shown that protein binding of meperidine [Ritschel et al.

1996a] and furosemide [Arancibia et al. 2003a] diminishes after exposure to high altitude even when albumin concentration is increased as an effect of exposure to altitude. In the case of furosemide, it was suggested that the increased free proportion of the drug could be due to an increased level of bilirubin observed in the group exposed to a high altitude. Considering these facts, one would expect a reduction in protein binding after exposure to high altitude. However, the physiological changes produced by exposure to a high altitude environment are extremely complex and not completely understood and more studies are required.

An increased number of red blood cells is a well-known consequence of exposure to a high altitude. In our study, the hematocrit was significantly higher in groups HA and HC, when compared to the group at sea level. Binding of prednisolone to erythrocytes has not been reported previously. We found 43.7 ± 14.6% binding to erythrocytes in the group at sea level with a rise to 50.6 ± 12.1% in the HA group and to 61.6 ± 12.6% in group HC. The latter values were found to be statistically different. The effect of high-altitude acclimatization on erythrocytes is also complex. For example, volume expansion and changes in permeability have been described [Grover et al. 1986, Sawaka et al. 1996]. Nevertheless, the increased binding in the HC group may be explained by the increased hematocrit in this group. The increased binding to erythrocytes explains the lower volume of distribution observed in groups exposed to a high altitude. The binding to erythrocytes may also be the cause of the reduced clearance in groups HA and HC.

Urinary excretion of prednisolone was completed after 24 hours and was significantly increased in group HA. On the other hand, excretion of prednisone was also higher in this group and reduced in group HC. The prednisolone/prednisone ratio in the urine was 11.1 in the sea level group, 7.3 in group HA and 45.6 in group HC. The concentration of prednisone in plasma or in whole blood was not measured because the concentrations were below the limit of quantification of prednisone in most of the samples. Our urinary excretion results, however, would indicate that chronic exposure to a high altitude would interfere in the prednisolone-prednisone interconversion. Since prednisone has very little intrinsic glucocorticoid activity and has to be converted to prednisolone for therapeutic effect, the alteration of the interconversion as a result of altitude exposure could have clinical relevance. Because the pharmacological action for corticosteroids is influenced by multiple factors in addition to pharmacokinetics, the therapeutic importance of this finding is difficult to conclude. Additional experiments are required to further evaluate the clinical implication of high-altitude exposure on the pharmacokinetics of prednisolone.

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